Long-Term Efficacy of Routine Access to Antiretroviral-Resistance Testing in HIV Type 1–Infected Patients: Results of the Clinical Efficacy of Resistance Testing Trial

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The long-term efficacy of making resistance testing routinely available to clinicians has not been established. We conducted a clinical trial at 6 US military hospitals in which volunteers infected with human immunodeficiency virus type–1 were randomized to have routine access to phenotype resistance testing (PT arm), access to genotype resistance testing (GT arm), or no access to either test (VB arm). The primary outcome measure was time to persistent treatment failure despite change(s) in antiretroviral therapy (ART) regimen. Overall, routine access to resistance testing did not significantly increase the time to end point. Time to end point was significantly prolonged in the PT arm for subjects with a history of treatment with $\geq$4 different ART regimens or a history of treatment with nonnucleoside reverse-transcriptase inhibitors before the study, compared with that in the VB arm. These results suggest that routine access to resistance testing can improve long-term virologic outcomes in HIV-infected patients who are treatment experienced but may not impact outcome in patients who are naive to or have had limited experience with ART.

Resistance to antiretroviral therapy (ART) is an important cause of treatment failure in patients infected with HIV-1 [1]. Resistance to ART has also been noted in HIV isolates recovered from treatment-naive, newly infected patients [2–4], with a prevalence that appears to be increasing [5].

There are 2 types of assays available for measurement of ART resistance. Genotype tests identify polymorphisms in the HIV genome associated with resistance, and phenotype tests measure ART susceptibility in vitro. Genetic polymorphisms associated with drug resistance have been retrospectively shown to be associated with treatment failure, development of AIDS, and

Received 2 September 2003; accepted 7 October 2003; electronically published 6 February 2004.

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Clinical Infectious Diseases 2004;38:723–30

1058-4838/2004/3805-0017$15.00

Financial support: Cooperative agreement (DAMD17-93-V-3004) between the US Army Medical Research and Materiel Command and the Henry M. Jackson Foundation for the Advancement of Military Medicine.

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The views and opinions expressed herein are those of the authors and do not purport to reflect the official policy or position of the US Army, Navy, Air Force, or Department of Defense.

Report Documentation Page

Form Approved
OMB No. 0704-0188

1. REPORT DATE	2. REPORT TYPE	3. DATES COVERED
2004	**N/A**	**-**

4. TITLE AND SUBTITLE	5a. CONTRACT NUMBER
Long-Term Efficacy of Routine Access to Antiretrovial-Resistance Testing in HIV Type 1-Infected Patients: Results of the Clinical Efficacy of Resistance Testing Trial	5b. GRANT NUMBER
	5c. PROGRAM ELEMENT NUMBER
6. AUTHOR(S)	5d. PROJECT NUMBER
	5e. TASK NUMBER
	5f. WORK UNIT NUMBER
7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES) **Naval Submarine Medical Research Laboratory Naval Submarine Base New London Box 900 Bldg 148, Trout Avenue Groton, CT 06349-5900**	8. PERFORMING ORGANIZATION REPORT NUMBER
9. SPONSORING/MONITORING AGENCY NAME(S) AND ADDRESS(ES)	10. SPONSOR/MONITOR'S ACRONYM(S)
	11. SPONSOR/MONITOR'S REPORT NUMBER(S)

12. DISTRIBUTION/AVAILABILITY STATEMENT
Approved for public release, distribution unlimited

13. SUPPLEMENTARY NOTES

14. ABSTRACT

15. SUBJECT TERMS

16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT	18. NUMBER OF PAGES	19a. NAME OF RESPONSIBLE PERSON
a. REPORT	b. ABSTRACT	c. THIS PAGE			
unclassified	**unclassified**	**unclassified**	**SAR**	**8**	

death [6–10]. Several prospective studies have shown short-term improvement in virus load (VL) suppression in patients when genotype testing [11, 12], phenotype testing [13], or genotyping with the advice of expert virologists [14] was used to guide therapy. Other recent studies showed either transient [15] or no benefit [16] associated with the use of resistance assays.

An International AIDS Society–USA panel has recommended that resistance testing be used to help guide ART selection at the time of treatment failure and that they be considered for treatment-naive patients at the time of therapy initiation [17]. The major impediment to the routine use of either genotype or phenotype assays is cost ($400–$1000 per assay), which is outside of the range of affordability for many HIV-infected patients. A more fundamental concern is the lack of information about the long-term efficacy of the routine use of resistance tests in the management of HIV-1 infection.

We conducted a prospective, randomized, multicenter study comparing the therapeutic efficacy of routine access to and use of genotype and phenotype resistance testing and results with those for clinical management without resistance testing in a cohort of HIV-1–infected beneficiaries of US Department of Defense (DoD) health care. The study's goal was to determine the long-term efficacy of routinely available resistance testing, as defined by an increase in the time to refractory treatment failure. Emulation of actual clinical practice patterns was reflected in the study design. Results from commercially available resistance tests were provided to treating clinicians without expert recommendations regarding test interpretation.

METHODS

Participants

HIV-1–infected beneficiaries of DoD health care were eligible for the Centers for Education and Research on Therapeutics (CERT) study if they were ⩾18 years of age, were receiving a stable ART regimen containing ⩾2 drugs for at least 8 weeks before randomization, were able to provide informed consent, and were willing to attend regular study visits. Participating centers were the following DoD tertiary care facilities: Walter Reed Army Medical Center (Washington, DC), National Naval Medical Center (Bethesda, MD), Naval Medical Center (Portsmouth, VA), Wilford Hall Air Force Medical Center and Brook Army Medical Center (San Antonio, TX), and Naval Medical Center (San Diego, CA). Volunteers were recruited by direct inquiry from treating clinicians at these centers.

Study Regimens and Randomization

The protocols and consent forms were approved by the institutional review boards of each participating institution and by the Tri-Service Human Subjects Research Review Board. Eligible volunteers were randomly assigned to 1 of 3 study arms: those with routine access to phenotype resistance testing (PT arm) or genotype resistance testing (GT arm) and those without such access (VB arm). A total of 611 patients were screened from October 1998 through October 2000, of whom 450 were randomized. Active study follow-up continued until October 2001. The randomization procedure was developed and performed centrally at the US Military Research Program Data Coordinating and Analysis Center (DCAC). Volunteers were randomized using a permuted block algorithm stratified by study site and Centers for Disease Control and Prevention (CDC) HIV disease stage.

Study algorithm. The study algorithm was designed so that end points would signify refractory treatment failure. To reach an end point, a participant would have to have treatment failure that was persistent, despite changes in therapy that were guided in the GT and PT study arms by results of resistance tests.

Routine study visits. Participants were evaluated at routine study visits every 3–4 months. At each visit, plasma VL was measured using the Roche Amplicor ultrasensitive assay (Roche Molecular Systems), which has a lower detection limit of 50 copies/mL.

Treatment failure criteria. Treatment failure was defined as a VL of >3.0 $\log_{10}$ copies/mL concomitant with ⩾1 of the following conditions: <1.0 $\log_{10}$ reduction in VL 4 weeks after starting a therapy regimen, failure to suppress VL to <200 copies/mL 6 weeks after starting therapy, detection of a plasma VL of >3.0 $\log_{10}$ copies/mL after initial suppression to <200 copies/mL, or an increase of >0.5 $\log_{10}$ copies/mL (to >3.0 $\log_{10}$ copies/mL) from the nadir VL that could not be directly attributed to vaccination or intercurrent illness. The lower limit of 3.0 $\log_{10}$ copies/mL was chosen to minimize the effects of VL "blips" on the conduct of the study and to reflect the performance limits of the resistance assays. Failure criteria were not mutually exclusive.

Confirmation of treatment failures. All treatment failures were confirmed with a second VL measurement during a confirmation visit 10–14 days later.

Changing failing therapy regimens. Upon confirmation of treatment failure, the treating clinician was offered the opportunity to make changes in the participant's drug regimen. No changes were mandated by the protocol.

Reevaluation of therapy changes and study end points. Four to 6 weeks after a confirmed treatment failure, the participant returned for reevaluation to determine whether failure persisted, despite therapy changes. If failure was found to persist, a study end point was attained. If the failure had resolved, no end point was attained, and the participant was asked to return in 3–4 months for another routine visit. To reach an end point, 2 consecutive confirmed treatment failures—deter-

mined during a routine visit and a subsequent reevaluation visit—were required.

For participants in the PT arm, an Antivirogram phenotype assay (Virco) was performed during each routine visit if the VL was >3.0 $\log_{10}$ copies/mL. For participants in the GT arm, a commercially available genotype assay was performed during each routine visit if the VL was >3.0 $\log_{10}$ copies/mL. From study initiation until June 2000, the Vircogen assay (Virco) was used in the GT arm. After this date, the Virtual Phenotype interpretation method (Virco) was added. Details about the assays have been published elsewhere [18–20].

Statistical Analysis

The primary analysis in this study was the pair-wise comparison of differences in times to end point between study arms (VB vs. GT and VB vs. PT). Secondary analyses compared times to end point between study arms, grouping participants according to previous ART exposure. The primary efficacy variable was time to end point, which was defined as time from study randomization through time to protocol-defined study end point, study discontinuation, or loss to follow-up. Right-censoring of time to event was performed for participants who were still active in the study and for those who had not reached a protocol-defined end point at the time of data analyses. All analyses were performed according to the intent-to-treat (ITT) principle: end points for all participants who were terminated from the study because of consent withdrawal, loss to follow-up, relocation away from the study site, medical reasons, or a protocol violation were specified as the date on which study participation ended. The ITT population comprised all randomized participants who underwent ⩾1 follow-up assessment.

Baseline variables were compared among study arms using Student t test and χ^2 analysis for continuous and categorical variables, respectively. Nonparametric product-limit estimation (Kaplan-Meier) was used to estimate the time to end point survival function in each study arm. The Wilcoxon log rank test was used to compare time to end point between study arms.

The Hochberg method (a modified Bonferroni procedure) was used to retain an overall 2-sided type I error rate of .05 during multiple comparisons of the primary and secondary end points, as described elsewhere [21]. This method rejected both null hypotheses if and only if the largest P value obtained was ⩽.05 (2-sided). Otherwise, the smallest P value obtained had to be ⩽.025 to be considered statistically significant with respect to the respective null hypothesis.

Univariate and multivariate Cox proportional hazards regression models were used to evaluate the effects of study arm, age, sex, race, CDC stage, exposure to nonnucleoside reverse-transcriptase inhibitors (NNRTIs), initial plasma HIV RNA load, and prestudy ART experience. Statistical analyses were performed using SPLUS 6, version 2 for Windows (Insightful).

Data Collection, Management, and Quality Assurance

All data were collected on standardized case report forms by certified clinical research coordinators, according to standardized Good Clinical Practice study procedures. Study data were entered into a central database maintained by DCAC. Double data-entry techniques, routine database checks, and frequent site visits ensured data quality.

RESULTS

Baseline clinical and demographic characteristics. Baseline demographic characteristics, HIV disease characteristics, and treatment histories of study volunteers are summarized in table 1. There were no significant interarm differences in any of the baseline characteristics except for age, which was slightly higher in the GT arm

ART history at study entry. All volunteers were ART experienced, with a mean history of exposure to 3.9 drugs (range, 3.6–4.2 days). Volunteers had a mean history of exposure to 2.4 nucleoside reverse-transcriptase inhibitors (NRTIs), 0.3 NNRTIs, and 1.2 protease inhibitors (PIs); 351 (78%) were NNRTI naive. One hundred forty-three (31.8%) volunteers had a history of treatment with >2 PIs at the time of enrollment. The most common combinations of drugs were stavudine-lamivudine-nelfinavir ($n = 52$) and zidovudine-lamivudine-nelfinavir ($n = 43$). Pre-enrollment ART history, by study arm and drug type, is shown in table 1.

Study discontinuations. A total of 128 volunteers discontinued participation in the study for reasons other than having reached a study end point (figure 1). There were no significant pair-wise differences in the number of non–end point discontinuations, time to non–end point discontinuation, or in the VL at time of discontinuation.

Primary outcome: time to refractory treatment failure. Median and mean times, respectively, to end point or censoring were 621 and 585 days for the VB arm, 668 and 799 days for the GT arm, and 683 and 736 days for the PT arm. There were no significant differences in mean time to end point among study arms (figure 2).

A secondary analysis was performed to compare time to event between study arms for volunteers who had an ART history of <4 drugs. This analysis demonstrated that there were no significant pair-wise differences in time to end point between study arms ($P = .36$ for VB vs. GT arms, and $P = .07$ for VB vs. PT arms). For volunteers with a history of receipt of ⩾4 ART drugs before enrollment, there was a notable increase in time to end point in the PT arm ($P = .043$) but not in the GT arm ($P = .553$), compared with the VB arm (figure 3, *right*).

Table 1. Baseline demographic and clinical characteristics of 450 participants in the Clinical Efficacy of Resistance Testing Trial who had no access to testing (VB arm) or who had access to genotype testing (GT arm) phenotype testing (PT arm).

Characteristic	GT arm (n = 151)	PT arm (n = 152)	VB arm (n = 147)
Percentage of total enrollment	33.6	33.8	32.7
Sex			
Female	18 (11.9)	23 (15.1)	16 (10.9)
Male	133 (88.1)	129 (84.9)	131 (89.1)
Race[a]			
African American	61 (40.4)	53 (34.9)	56 (38.1)
Asian	0 (0)	3 (2.0)	6 (4.1)
White	72 (47.7)	83 (54.6)	73 (49.7)
Hispanic	18 (11.9)	12 (7.9)	10 (6.8)
Other/not specified	0 (0)	1 (0.7)	2 (1.4)
Age,[b] mean years ± SD	39.8 ± 8.8	37.8 ± 7.9	37.5 ± 9.0
CDC HIV stage			
A	103 (68.2)	104 (68.4)	93 (63.2)
B	21 (13.9)	26 (17.1)	22 (15.0)
C	27 (17.9)	22 (14.5)	32 (21.8)
CD4 cell count, mean cells/mL ± SD	478.0 ± 265.3	498.8 ± 279.2	436.1 ± 241.7
Virus load, mean $\log_{10}$ copies/mL ± SD	2.7 ± 1.1	2.7 ± 1.1	2.8 ± 1.2
Mean number of ARVs received	3.42	3.49	3.23
Protease inhibitors, no. received			
⩽2	105 (69.5)	98 (64.5)	104 (70.7)
>2	46 (30.5)	54 (35.5)	43 (29.3)
ARV history, mean no. received			
Protease inhibitors	1.14	1.40	1.38
NNRTIs	0.23	0.28	0.27
NRTIs	2.44	2.55	2.18
Total	3.81	4.23	3.63
NNRTI experienced	31	35	33

NOTE. Data are no. (%) of patients at enrollment, unless otherwise indicated. Categorical variables were compared using χ^2 analysis, and continuous variable were compared using Student's t test. ARV, antiretroviral; CDC, Centers for Disease Control and Prevention; NNRTI, nonnucleoside reverse-transcriptase inhibitor; NRTI, nucleoside reverse-transcriptase inhibitor.

[a] Self-reported.

[b] $P < .05$

There were no significant pair-wise differences in time to end point between study arms for volunteers who were NNRTI naive at enrollment ($P = .90$ for VB vs. GT arms, and $P = .83$ for VB vs. PT arms). Compared with the VB arm, there was a significant increase in time to end point in the PT arm ($P = .01$) but not the GT arm ($P = .10$) for volunteers who were NNRTI experienced at enrollment (figure 3, *left*).

A univariate Cox regression analysis (table 2) demonstrated that, in the subset of NNRTI-experienced subjects, the risk of treatment failure was 1.82 times greater in the VB arm than in the GT arm ($P = .044$) and 2.7 times greater in the VB arm than in the PT arm ($P = .002$). In the subset of subjects with a treatment history of ⩾4 ART drugs, risk of treatment failure in the VB arm was 1.75 and 1.69 times greater than the risk in the GT ($P = .010$) and PT ($P = .010$) arms, respectively.

Treatment changes during study. The mean numbers of ARTs received during the study were 4.12, 4.68, and 4.72 in the VB, GT, and PT arms, respectively. There were no significant pair-wise differences in the numbers of NRTIs, NNRTIs, or PIs received during study participation.

Resistance tests performed during the study. A total of 75 subjects in the GT arm and 74 subjects in the PT arm never had a VL of >3.0 $\log_{10}$ copies/mL during the study and, consequently, had no resistance tests performed. Thirty-six subjects

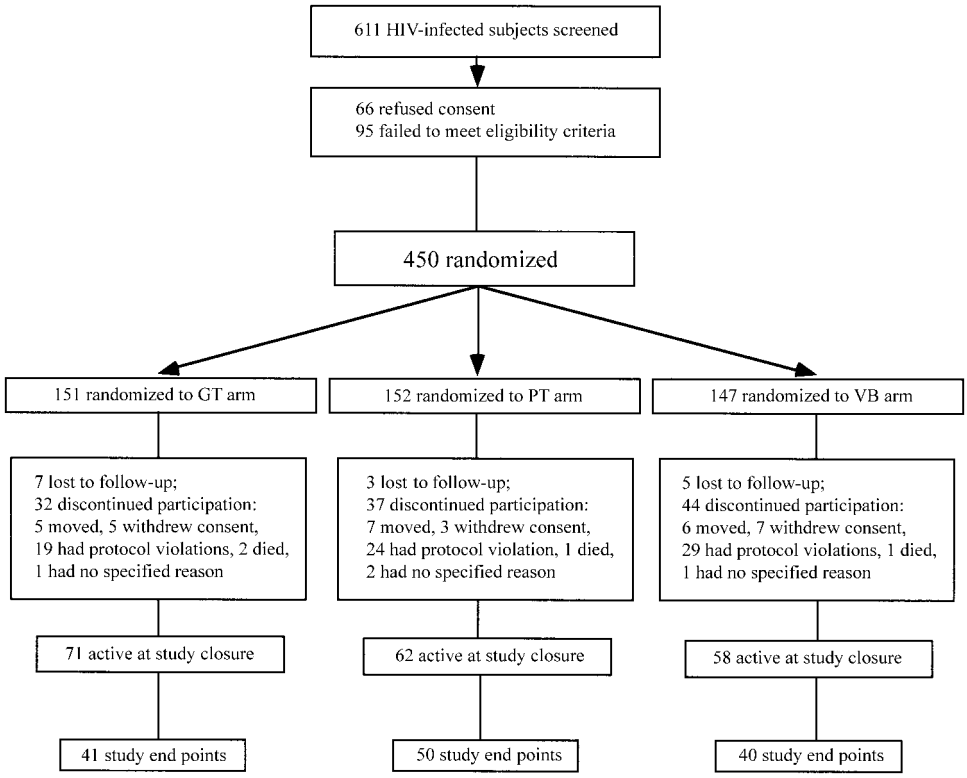

Figure 1. Flow chart of the Clinical Efficacy of Resistance Testing study involving the following 3 groups: patients with routine access to phenotype resistance testing (PT arm) or genotype resistance testing (GT arm) and patients without such access (VB arm).

in the GT arm and 26 subjects in the PT arm underwent ⩾1 resistance test but never reached a study end point. The mean turn-around times for the resistance assays were 5 and 21 working days for the genotype and phenotype assays, respectively.

DISCUSSION

The purpose of the CERT study was to determine the long-term efficacy of the routine access to resistance testing in a realistic clinical practice setting through the use of commercially available resistance tests and a study algorithm modeled after standard of care. This study design differs from those of several previous studies, which addressed the impact of resistance testing on relatively short-term virologic end points in highly structured clinical settings. Because of the unique design of our study, which was intended to assess long-term impact of access to resistance testing, direct outcomes comparisons with other studies is difficult.

Several previously published prospective studies have shown a benefit to be associated with resistance testing [11–13]. Two studies have suggested that the benefit of resistance testing is increased when expert interpretation of the resistance test results is used to guide therapy changes [12, 14], although a third study, which included a cohort of predominately heavily pretreated patients, failed to show even relatively short-term virologic improvement with the use of either phenotype or genotype resistance tests in combination with expert advice [16].

The CERT study did not show that an overall improvement in the time to refractory treatment failure was associated with routine access to either genotype or phenotype resistance testing, when used in a cohort of patients with a large number of enrollees with limited previous ART exposure. Causes of long-term treatment failure other than resistance, such as incomplete adherence to therapy and pharmacokinetic factors, compromise the power to accurately assess the impact of resistance testing, even in large studies such as CERT. In addition, the CERT cohort had many subjects who never experienced treatment failure and, thus, never required resistance testing, which also limits the study's power.

Nonetheless, in the subset of CERT volunteers with relatively more ART experience, therapy changes guided by phenotype resistance testing prolonged the time to refractory treatment failure. This subgroup likely includes a higher prevalence of drug resistance, which would have the effect of potentially increasing the benefits associated with testing.

No benefit from the routine access to genotype testing was observed in the primary analysis of this study, although univariate Cox regression analysis showed modest but statistically

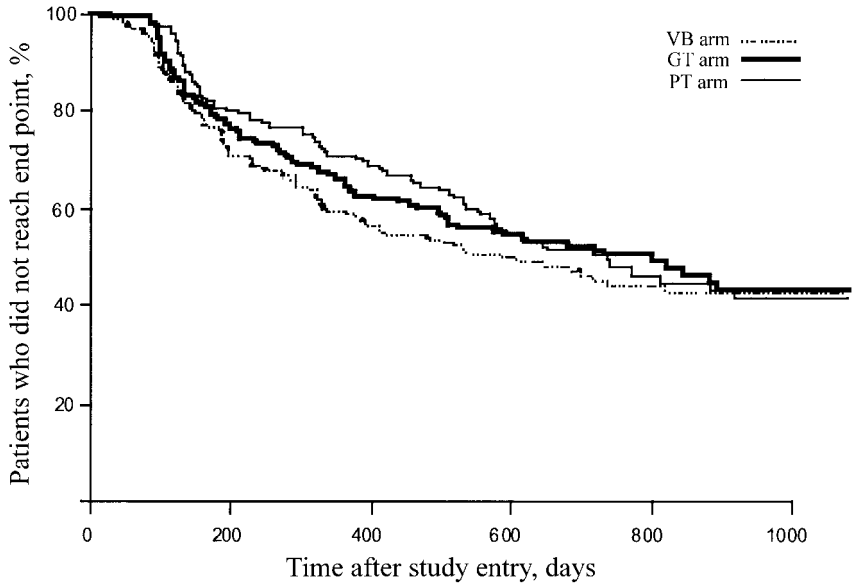

Figure 2. Estimated time to end point curves in the intent-to-treat analysis involving the following 3 groups: patients with routine access to phenotype resistance testing (PT arm) or genotype resistance testing (GT arm) and patients without such access (VB arm). The estimated percentage of subjects not reaching the end point is represented on the y axis, and the time to end point is represented on the x axis. Two-arm survival comparisons using log-rank and χ^2 tests resulted in *P* values of .39 (VB vs. GT arms) and .29 (VB vs. PT arms).

significant differences in hazard ratios between the VB and GT arms for volunteers with a history of ⩾4 ARTs or NNRTI experience before enrollment. The relative lack of benefit from readily available genotype testing results in the CERT study is at odds with the results of some of the other previously published studies mentioned above, with the exception of the NARVAL study [28]. Most of the other studies have assessed short-term changes in viral burden, in contrast to the long-term

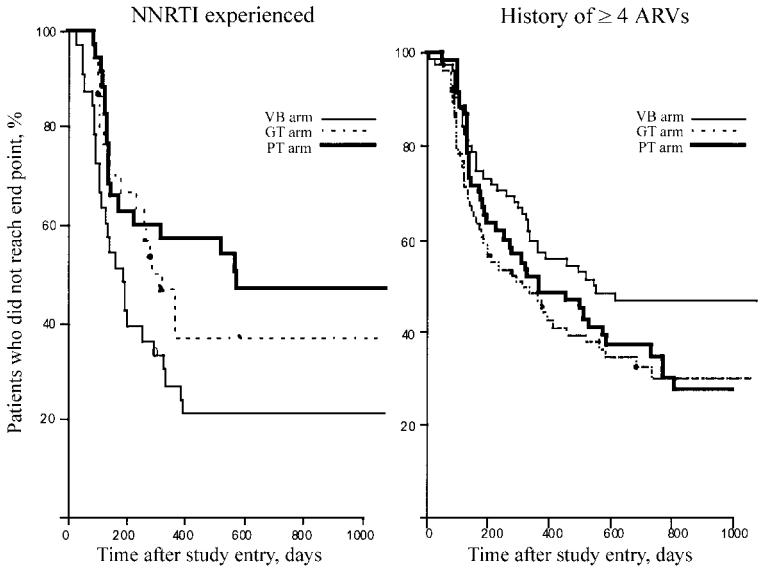

Figure 3. Estimated time to end point curves for participants who had a history of treatment with nonnucleoside reverse-transcriptase inhibitors (NNRTIs) *(left)* or ⩾4 antiretroviral (ART) agents before study enrollment (*right;* the time to end point in NNRTI-experienced subjects is indicated). Log-rank pairwise comparisons for the NNRTI-experienced subgroup yielded *P* values of .1 (patients without access to testing [VB] vs. patients with access to genotype testing [GT]) and .01 (VB vs. patients with access to phenotype testing [PT]). For the ART-experienced subgroup, pairwise comparisons using the log-rank test resulted in *P* values of .55 (VB vs. GT arms) and .04 (VB vs. PT arms).

Table 2. Univariate Cox proportional hazard ratios representing the risk of reaching a study end point for subjects who had no access to testing (VB arm), compared with those who had access to genotype testing (GT arm) or phenotype testing (PT arm).

	VB vs. GT arms		VB vs. PT arms	
Variable	Hazard ratio (95% CI)	P^a	Hazard ratio (95% CI)	P^a
NNRTI history before study entry				
Naive	0.98 (0.68–0.70)	NS	0.97 (0.67–1.39)	NS
Experienced	1.82 (1.02–3.33)	.04	2.7 (1.45–5.00)	<.01
ARV history, no. received				
<4	0.75 (0.48–1.19)	NS	0.93 (0.58–1.52)	NS
⩾4	1.75 (1.15–2.7)	.01	1.69 (1.12–2.56)	.01

NOTE. A hazard ratio >1 indicates an increased risk of reaching a study end point for subjects in the VB arm. ARV, antiretroviral; NNRTI, nonnucleoside reverse-transcriptase inhibitor; NS, not significant.

[a] By the Wald Test. $P \leqslant .05$ was considered to be statistically significant.

efficacy end point of the CERT study. In addition, all subjects in the resistance-testing arms of these studies underwent testing, in contrast to the patients in the CERT study.

Another possible reason for the inability to show durable benefits associated with genotype-guided therapy is that the interpretation of mutation patterns is inherently complex. In the absence of selective therapy pressure, virus variants with resistance-conferring mutations may rapidly be outcompeted by wild-type strains, causing them to be undetectable by current assays [22]. Consequently, a clinician may falsely conclude that a virus is susceptible to a given drug. However, when that drug is reintroduced, the virus variants with resistance-conferring mutations will rapidly reemerge and lead to therapy failure. The interactions between mutations to confer cross-resistance or to suppress the effect of other mutations have been extensively reviewed elsewhere [17]. Several different strategies for the interpretation of viral mutation patterns have been developed and compared [23–26]. In the CERT study, a commercially available, algorithm-based strategy was initially used for the interpretation of genotypes. An interpretation strategy based on a relational database of genotypes and phenotypes was employed when it became available in June 2000. It is difficult to assess the impact of these different methods on the overall outcome of the study. Furthermore, the ability to compare different studies that assessed the impact of genotype-based management is impaired by the variety of interpretation methods employed. There are retrospective data to suggest that use of the relational database strategy is a better predictor of clinical outcome than are algorithm-based methods [27], but this approach has not been assessed prospectively. Potential advantages of genotype testing over phenotype testing include more rapid turn-around time, decreased cost, and the ability to perform the tests in many laboratories, rather than a few highly specialized central facilities.

The results of the NARVAL study indicated that clinicians might prescribe fewer drugs at the time of treatment failure when resistance results are available. Indeed, in a recent analysis, the NARVAL group suggested that, for patients with extensive prior ART exposure who did not respond to HAART, resistance testing was cost-effective when the sparing of future drug costs was considered [28]. In contrast, the CERT study found no differences in the number of ARTs prescribed to volunteers in any of the 3 arms during the course of the study.

Cost is a central issue in the debate on the use of resistance tests. The cost-effectiveness of resistance testing has been demonstrated in a retrospective study [29]. Nevertheless, the offset of cost of testing compared with the reduction in drug costs did not reach statistical significance in an economic analysis in the VIRADAPT study [30]. The results from the CERT study suggest that use of resistance testing could be limited to patients who have at least some history of previous ART exposure, which may potentially decrease the overall cost burden without loss of clinical effect.

In conclusion, the CERT study shows that a long-term benefit of the availability of resistance testing results for patients with a history of NNRTI therapy or exposure to ⩾4 ARTs but not for those with a less complex treatment history. Because of the cost of resistance assays, additional analysis of the economic impact of their widespread use is warranted.

THE RV-125 CENTERS FOR EDUCATION AND RESEARCH ON THERAPEUTICS STUDY TEAM

Susan Banks, Anthony Barile, Kim Blankenship, Faith Butler, Linda Coelho, John Cooley, Robin Darden, Kathleen Duffy, Kamal Dyal, Wes Emmons, Hannah Flaks, Robin Garner, Sheila Hopper, Don Johnson, Jim Lane, Laura Lin, Terry Merritt, Walter Mika, Diane Plentovich, and Maria Villarroel.

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